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Lt. Gen. Jeffrey G. Smith, U. S. A. (Ret.)
Director of Government Relations

AUG 24

August 23, 1990

Mr. William K. Reilly
Administrator
The United States Environmental
Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Re: Ethyl HiTEC® 3000, Docket A-90-16

Dear Mr. Reilly:

Transmitted herewith are supplemental reply comments to late-filed comments on the public health effects of HiTEC® 3000. In particular, these supplemental reply comments respond to comments filed by two staff members of the National Institute of Environmental Health Sciences. Since their comments are dated July 23, 1990, it is clear that these commentators filed their comments without the benefit of reviewing Ethyl Corporation's July 23 submittal addressing the public health implications of the Additive in extensive detail.

Ethyl notes that EPA has met with several of the commentators in this proceeding and looks forward to a similar opportunity to meet with EPA after the Agency has reviewed all of Ethyl's comments.

Sincerely,

Jeffrey G. Smith

A-90-16
IV-D-139

BEFORE THE
UNITED STATES
ENVIRONMENTAL PROTECTION AGENCY

IN RE APPLICATION FOR A FUEL ADDITIVE WAIVER FILED BY ETHYL CORPORATION UNDER § 211(f)(4) OF THE CLEAN AIR ACT	)))))))

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SUPPLEMENTAL REPLY OF ETHYL CORPORATION TO LATE-FILED COMMENTS ON PUBLIC HEALTH EFFECTS OF HITEC® 3000

Submitted by:

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August 23, 1990

SUMMARY

Ethyl Corporation ("Ethyl") is seeking a waiver for use of HiTEC® 3000 Performance Additive (the "Additive") in unleaded gasoline in the U.S. Most of the comments filed with EPA support approval of the waiver. The limited number of commentators who have raised questions about the waiver fall into two categories -- those concerned about the Additive's effect on automobile emission control systems and those concerned about the public health implications of the Additive. Ethyl has exhaustively responded to both of these issues in this proceeding.

In late-filed comments, two staff members of the National Institute of Environmental Health Sciences ("NIEHS") have raised questions addressing use of the Additive and public health. These questions are essentially the same questions Ethyl has already responded to in its extensive health submittals. Because it is clear from the NIEHS staff members' comments, however, that they did not have the opportunity to review Ethyl's detailed July 23 health submittal <u>before</u> filing their comments, Ethyl briefly responds to their questions in these supplemental comments.

In particular, Ethyl has shown that environmental levels of manganese associated with use of the Additive will remain at a level far below those associated with any potential adverse public health effects, even applying unrealistically conservative assumptions about the manganese emitted from automobiles using the Additive. The marginal increase in exposure to manganese associated with use of the Additive would be well within the existing range of dietary variability for manganese. The NIEHS

staff members' concern about the lack of definitive dose/response data for manganese is therefore unwarranted.

As recognized by numerous independent governmental reviews of the health implications of manganese emissions, the minute changes which the Additive would cause in current environmental levels of manganese would present no public health concern:

- In 1985, EPA issued a final "Health Assessment Document for Manganese," and concluded that low levels of manganese in the environment will not "cause, or contribute to, air pollution which may reasonably be anticipated to result in an increase in mortality or an increase in serious illness."

- In September 1988, the Health Effects Institute (HEI) completed another independent review of the health literature on manganese, and HEI concluded that no adverse health effects (neurological or respiratory) would occur even at manganese emission levels one hundred times higher than those that would result from use of the Additive.

- Based on its review of the health effects of manganese, the Canadian Department of National Health and Welfare concluded in 1978 that "there is no evidence at present to indicate that expected ambient manganese concentrations [from automobile exhaust] would constitute a hazard to human health."

- In 1986, the Royal Society of Canada again reviewed the health literature and concluded that "the general public has a wide margin of health safety with respect to the worst case use of MMT in gasoline."

- In 1987, an official from Australia's Department of Health completed an independent evaluation of the public health effects of manganese, and concluded that "there is no toxicological evidence to suggest that the increased level of airborne Mn resulting from combustion of MMT as a petrol additive is likely to constitute a health risk to the general population."

- Based on its review of the literature, the World Health Organization has concluded that an annual average concentration of 1 ug/m^3 -- about ten to one hundred times higher than maximum urban ambient concentrations associated with use of the Additive -- "incorporates a sufficient margin of protection for the most sensitive population group."

Indeed, because of the significant reductions in pollutants such as carbon monoxide, oxides of nitrogen, benzene, and formaldehyde, use of the Additive will have a significant benefical impact on public health.

TABLE OF CONTENTS

Attachments

1. Letter and attachments from Dr. H. Daniel Roth to Dr. Donald Lynam dated August 23, 1990
2. Letter from Dr. W. Clark Cooper to Dr. Donald Lynam dated August 17, 1990
3. The Additive and Dermal Exposure
4. Road Load Particulate Emissions

I. INTRODUCTION

Ethyl Corporation ("Ethyl") has filed an application with the U.S. Environmental Protection Agency ("EPA" or the "Agency") for a waiver under § 211(f)(4) of the Clean Air Act ("Act") to permit the use of HiTEC® 3000 Performance Additive ("the Additive") at a concentration of 0.03125 grams manganese per gallon of unleaded gasoline. EPA held a public hearing on June 22, 1990 on Ethyl's application, and has received a large number of written comments on the waiver request, the overwhelming number of which support approval of the application.[1/]

On August 1, 1990, EPA received additional comments (dated July 23, 1990) from two staff members of the National Institute of Environmental Health Sciences ("NIEHS"), restating, in effect, the public health questions raised generally by NIEHS in a memorandum to the Agency dated June 7, 1990.[2/] The comments of these staff members (hereinafter "Dr. Fouts") were not placed into the public docket for this proceeding until August 20, 1990.

[1/] Responding to the limited number of questions raised about the application, Ethyl filed supplemental comments on its application on July 23, 1990 (the close of the official comment period), and on August 10, 1990. The comments filed by Ethyl on July 23 exhaustively addressed, among other things, public health concerns. <u>See</u> Comments in Support of the Waiver Application for the HiTEC® 3000 Performance Additive filed by Ethyl Corporation (July 23, 1990)[hereinafter "Ethyl Comments"]. In its comments filed on August 10, Ethyl responded to various concerns raised by automobile industry commentators. <u>See</u> Reply Comments of Ethyl Corporation in Support of the HiTEC® 3000 Waiver Application (August 10, 1990)[hereinafter "Reply Comments"].

[2/] <u>See</u> Memorandum from James R. Fouts, Senior Science Advisor to the Director, NIEHS and Kathryn R. Mahaffey, Research Chemist to Mary T. Smith, Field Operations & Support Division, EPA (July 23, 1990) [hereinafter "Fouts Memorandum"].

Ethyl responds below to Dr. Fouts' comments on the application. Ethyl's response is brief because the public health questions raised by Dr. Fouts have already been extensively addressed by Ethyl in this proceeding. As Dr. Fouts' comments are dated July 23, 1990, he would not have had the opportunity to review Ethyl's July 23 submission addressing the Additive's impact on public health before filing his comments. Therefore, in this response, Ethyl will either reference its earlier comments to the concerns specified by Dr. Fouts, or to the extent he expands upon an issue raised earlier or references a study not specifically addressed in Ethyl's July 23 submission, present an appropriate response.[3/]

[3/] Dr. Fouts has in several instances mischaracterized the findings and implications of studies cited in support of his assertions, or has made assertions unsupported by any citations. For example, he cites a study by Rehnberg et al. (1980) in support of the assertion that the "specific form of manganese produced by combustion of MMT, manganese tetroxide, has been found to be absorbed and retained to a greater extent than other manganese oxides/salts by young rats." Fouts Memorandum, Attachment at 11. In fact, Rehnberg et al. only reported on tests of Mn_3O_4 absorption, not on any other oxides or salts of manganese. Dr. Fouts also implies, citing a study by Cahill et al. (1980), that excessive absorption of manganese during infancy will result in permanently elevated levels of manganese in the brain and irreversible damage to neurons. Not only is there no evidence supporting either of these assumptions, the results of the Cahill study indicated that the retention of manganese in the brain was independent of the age at which the manganese was administered to the neonatal rat. Finally, the assertion that females may be more susceptible to the toxic effects of manganese (see id. at 11) is totally unsupported.

These and other assertions are addressed in the comments below, or in the attached letters from Dr. H. Daniel Roth and Dr. Clark Cooper. Together with Ethyl's extensive submission dated July 23, these materials address each of Dr. Fouts' concerns, and (continued...)

II. ETHYL HAS ALREADY ADDRESSED THE PUBLIC HEALTH QUESTIONS RAISED BY DR. FOUTS.

Dr. Fouts asserts three general health concerns associated with use of the Additive:

1. The pulmonary and neurotoxic effects of exposure to manganese;[4]

2. The potential effects of exposure to manganese on susceptible populations;[5]

3. The toxicity of the Additive following dermal exposure.[6]

In its prior submissions, Ethyl addressed each of these concerns, and has shown that use of the Additive will not adversely affect the public health.[7]

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[3] (...continued) show that use of the Additive will not adversely affect public health.

[4] Fouts Memorandum, Attachment at 1, 2-3, 7, and 8-9.

[5] Fouts Memorandum, Attachment at 3-4, 12-13.

[6] Fouts Memorandum, Attachment at 1, 4-5.

[7] For a discussion of the pulmonary effects of manganese, see In Re Application for a Fuel Additive Waiver Filed by Ethyl Corporation Under § 211(f)(4) of the Clean Air Act (May 9, 1990)[hereinafter "Waiver Application"], Appendix 8 at 11 (hereinafter "Health Appendix"); Ethyl Comments, Appendix 3 at B-3 to B-4, B-6 to B-8, C-8, D-6 to D-7 (hereinafter Roth Report). For a discussion of the neurotoxic effects of manganese, see Health Appendix at 11; Roth Report at B-2 to B-3, B-6, C-2 to C-9, D-2, D-4 to D-6. For a discussion of populations susceptible to manganese, see Roth Report at B-5, D-7. For a discussion of the toxicity of the Additive, itself, see Health Appendix at 13-15.

Indeed, the substantial reductions in pollutants such as carbon monoxide, oxides of nitrogen, benzene and formaldehyde associated with use of the Additive will enhance public health. See Roth Report at E-1 to E-5.

Not having had the benefit of reviewing Ethyl's July 23 submission, Dr. Fouts expresses the view that no definitive "time-course, dose-response/effect with neurotoxicity as the endpoint" exists for manganese,[8/] and states that "until this research need is met, granting the waiver requested by Ethyl should be delayed or denied."[9/]

The problem with Dr. Fouts comment is that it is based on a fundamental misconception -- i.e., that in the absence of definitive dose-response data, no reasonable judgment can be made about the public health implications of a marginal increase in exposure to manganese that is well within the existing range of dietary variability for manganese. This is not the case. The available health data on manganese support the conclusion that exposure to concentrations of manganese below a certain level cannot reasonably be anticipated to adversely affect the public health. Because the environmental levels of manganese associated with use of the Additive will remain at a level far below that associated with adverse public health effects, the waiver can be granted even in the absence of definitive knowledge of the dose/response relationship at higher concentrations.

EPA's decision in 1985 not to regulate manganese as a hazardous air pollutant under § 112 of the Act is a clear example of regulatory action in the absense of definitive knowledge of

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[8/] Fouts Memorandum, Attachment at 4.

[9/] Id.

the dose/response relationship. As a basis for that decision, EPA prepared a Health Assessment Document on manganese which found that "an accurate dose-response relationship for inhalation exposure and neurotoxicity is unobtainable at present."[10/] Notwithstanding this finding, EPA concluded, on the basis of existing data, that manganese in ambient air neither causes nor contributes to, nor "may reasonably be anticipated to result in," an increase in mortality or serious illness.[11/] This conclusion was based on the Agency's recognition:

> (1) That public exposure to manganese is presently far below any level associated with noncarcinogenic serious health effects, and (2) that evidence currently available does not indicate that manganese is a carcinogen.[12/]

EPA declined to regulate manganese emissions because it recognized that the data do not reasonably support an inference of adverse public health effects from manganese levels anywhere near those presently found in ambient air. Dr. Fouts has not cited any new data to call into question EPA's determination. Indeed, as discussed below, all of the independent health experts who have looked specifically at the public health implications of the Additive on Ethyl's behalf, as well as several governmental bodies, have concluded that its use will not adversely affect the public health.

10/ HAD at 6-45.

11/ *See* 42 U.S.C. § 7412(a)(1)(emphasis added).

12/ 50 Fed. Reg. 32,627 (1985) (emphasis added).

A. Possible Respiratory and Neurological Effects of Manganese

On Ethyl's behalf, a team of well-known public health experts assembled by Roth Associates, Inc. evaluated the potential adverse impacts on health from the concentrations of airborne manganese that would follow approval of Ethyl's waiver application. The results of this review, and other material on the risk of respiratory and neurological effects from use of the Additive, were reported by Ethyl in its July 23 submission.[13/] Roth Associates concluded that, while exposure to extremely high concentrations of manganese has clearly been associated with neurological and respiratory effects, "[t]he available epidemiological data indicate that manganese has neurotoxic and, perhaps, respiratory effects only at levels many times higher than those related to MMT usage" and that "examination of the epidemiological and toxicological data indicates that exposure to manganese at levels that would result from using MMT as a fuel additive will not pose a health threat."[14/] The conclusions of

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13/ *See* Ethyl Comments at 31-44 and Appendices 3, 4, 5, 6, and 7.

14/ Roth Report, Executive Summary at 3 (emphasis added).

A second late-filed comment, a letter from Dr. Robert G. Feldman also discusses neurotoxic effects of manganese. Dr. Feldman questions whether "the increase in numbers of cases of Parkinson's disease in modern society is related to greater levels of airborne neurotoxins, such as manganese?" Dr. Feldman cites no studies providing a basis for this speculation and, in fact, acknowledges that the histopathology of brains of victims of Parkinson's disease differs from that of brains of victims of manganism. The experts working with Roth previously evaluated (continued...)

other independent health experts, and various governmental bodies, are similar.[15/]

The Roth Associates experts were provided with a copy of Dr. Fouts' comments and asked whether anything in those comments caused them to alter their conclusion. As indicated in the attached letter from Dr. H. Daniel Roth, <u>the conclusion remains unchanged: manganese concentrations resulting from approval of</u>

[14/] (...continued)
the possibility of a link between Parkinson's disease and manganism. As the Roth Report indicates, not only the neuropathy, but the mechanism of manganism differs from that of Parkinson's disease. Roth Report at D-6, D-7 & Attachment D-4.

[15/] <u>See</u> Ethyl Comments, Appendix 7. <u>Dr. Henry Wisniewski</u>, for example, states that "in my judgment, Ethyl provided enough evidence to show that adding Mn to their products will not negatively affect human life and the environment." <u>Id.</u> Attachment 1 at 2. <u>Dr. Robert Lauwerys</u> agrees with the World Health Organization's conclusion that annual ambient manganese levels below 1 ug/m3 "should incorporate a sufficient margin of protection for the most sensitive population group." <u>Id.</u> Attachment 2 at 4. <u>Dr. W. Clark Cooper</u> stated that as of July 1990 he was not aware of any new studies that alter his opinion that the "minute increments of Mn that would result from the use of MMT as a gasoline additive should not have any impact on the public's health." <u>Id.</u> Attachment 4 at 2.

The <u>Canadian Department of Health and Welfare</u> concluded in 1978 that "there is no evidence at present to indicate that expected ambient manganese concentrations [from automobile exhaust] would constitute a hazard to human health." <u>Id.</u> Appendix 4 at iv. In 1986, the <u>Royal Society of Canada</u> again reviewed the health literature on manganese and concluded that, even after over eight years of use of the Additive in Canada at two times the concentration requested in this proceeding, "the general public has a wide margin of health safety with respect to the worst case use of MMT in gasoline." <u>Id.</u> Appendix 5 at 11. Finally, in 1987, the <u>Australian Department of Health</u> made a similar determination. <u>See id.</u> Appendix 6 ("there [are] no toxicological concerns over the use of MMT in petrol").

Ethyl's fuel waiver application will not endanger public health.[16/]

This conclusion is based on a reexamination of the relevant studies cited in the Fouts Memorandum. With regard to possible neurological effects, Roth indicates that the "studies cited by [Dr. Fouts] provide no evidence of health effects from low level exposure to manganese, since the levels are not given, and they are most likely high."[17/] Roth concludes:

> There have been studies reporting a lack of effect after moderate exposure (.17 ug/m3 - 2.3 mg/m3) to manganese . . . . Thus, it is far-fetched to believe that there would be neurological effects below 100 ug/m^3, . . . Considering that the quantity of manganese which would be added to the ambient air by MMT use is at least 10,000 times lower than this, there is more than adequate evidence that MMT use will not contribute to neurological effects.[18/]

With regard to potential pulmonary effects, Roth concludes that:

> [t]he amount of manganese which would be added to the ambient air from MMT use is 0.0009 ug/m3, which would not significantly increase the current average level of 0.03 ug/m3. Conservatively assuming a

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[16/] See Letter from H. Daniel Roth to Dr. Donald Lynam (Aug. 23, 1990) (Attachment 1 to these comments) [hereinafter the "Roth Letter"]

[17/] Roth letter at 4-5.

[18/] Roth Letter at 3 (emphasis added). Moreover, contrary to what Dr. Fouts implies, "[t]here is no reliable evidence that Mn3O4 [the primary combustion product of the Additive] is more toxic than other forms of manganese, nor is there evidence that human infants absorb and retain Mn3O4 more readily than other forms of manganese." Id. at 13.

> contribution from MMT of 0.09 ug/m3 would increase the ambient manganese level to 0.12 ug/m3, which is still 25 times lower than even the lowest level of manganese suggested by the [seriously flawed] Nogawa et al. study. The Kimbrough et al. (1989) article cited by NIEHS adds no information on respiratory effects, since it is only a listing of chemicals and not a research paper.[19/]

That emissions of manganese associated with use of the Additive will not pose a threat to health is confirmed by a comparison of nutritional requirements for the element with the daily intake of manganese that would be associated with use of the Additive. As recognized by Dr. Fouts, manganese is a "required nutrient."[20/] The National Research Council of the National Academy of Sciences has recommended a daily intake of 2-5 mg for adults and 0.6 mg for infants.[21/] Recently, the federal Food and Drug Administration proposed Reference Daily Intakes (RDIs) for manganese of 3.5 mg/day for adults and children over 4 (including pregnant women and lactating mothers), 1.3 mg/day for children between 1 and 4 years old and 0.6 mg/day for infants.[22/]

[19/] Roth Letter at 2.

[20/] Fouts Memorandum, Attachment at 13.

[21/] National Research Council, Recommended Daily Allowances, (10th ed. 1989).

[22/] 55 Fed. Reg. 29,476 (July 19, 1990). "RDI" is a redesignation of the term "U.S. Recommended Daily Dietary Allowance." RDIs reflect levels of intake "designed to meet the known nutritional needs of practically all healthy persons." Id. at 29,476, 29,478.

Dr. Fouts acknowledged that occasional daily intake as high as 10 mg can be considered safe.[23/]

By comparison, an individual would inhale approximately 0.00002 mg a day as a result of the proposed use of the Additive,[24/] over 100,000 times below the proposed RDI for adults.[25/] This comparison is highly conservative because it is based on the assumption that all inhaled manganese is taken into the body. In fact, most of the manganese would be expired or cleared through the gastrointestinal tract.[26/]

[23/] Fouts Memorandum, Attachment at 11. Dr. Fouts is in error when he suggests that manganese absorption in adults "is not under close homeostatic control." Id. at 10. Not only is this statement clearly contrary to the findings of the HAD (see HAD at 4-13), it is also inconsistent with Dr. Fouts' recognition that "[g]astrointestinal absorption is regulated in the adult." Id.

[24/] Roth Letter at 7 and Attachment B. This figure is based on an ambient manganese contribution from the Additive of 0.0009 ug/m^3, as calculated by Systems Applications , Inc. (see Waiver Application, Appendix 5 at 63-65) and a ventilation rate of 20 m^3/day.

[25/] The volume of air inspired by an infant per day can be approximated by comparing basal metabolic rates (BMR) of adults and infants. The BMR determines the oxygen requirements of, and therefore the amount of air inhaled by an individual. BMR can be estimated by the equation BMR = $3W^{0.75}$ (White, A., Handler, P. and Smith, E. L., Principles of Biochemistry, McGraw-Hill Book Company, N.Y. 4th Edition at 297). According to this equation, the BMR of a 70 kg adult is 72.6 Cal/hr while that of a 5 kg infant is 10 Cal/hr. This means that an infant would inhale about 1/7 the volume of air/day relative to that inhaled by an adult, or about 3 m^3/day. The total amount of manganese from HiTEC usage inhaled by the infant would be about 0.000003 ug or more than 100,000 times below the proposed RDI for infants of .06 mg/day.

[26/] The manganese particles emitted in exhaust from automobiles fueled with gasoline containing the Additive which remain

(continued...)

Furthermore, the manganese intake attributable to use of the Additive would be far lower than manganese intake from other sources. If manganese intake associated with the Additive is added to total average adult manganese intake from food, air and water, the average daily intake of manganese would increase from approximately 3.30860 mg to approximately 3.30862 mg.[27/] In other words, the Additive would increase the average daily intake of manganese by 0.0005 percent.[28/] And the average total manganese intake even with use of the Additive would still be below the

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[26/] (...continued) airborne have a mass median equivalent diameter of about 0.3 micrometers. See Ethyl Comments at 20-21, n. 45. EPA documents indicate that deposition of 0.3 micrometer particles in the alveolar region of the lung is less than 30%. See EPA, Second Addendum to Air Quality Criteria for Particulate Matter and Sulfur Oxides (1982): Assessment of Newly Available Health Effects Information 2-3 (December 1986). The remaining 70% of the particulate mass would be expired or cleared to the gastrointestinal tract. Three to four percent of the particles cleared to the gastrointestinal tract would be absorbed through the intestine. HAD at 4-26. The remainder would be excreted in the feces.

[27/] Roth Letter at 7 and Attachment B.

[28/] Roth Letter at Attachment B. For purposes of conservatism, Roth also did his analyses assuming that the contribution of the Additive to ambient manganese levels was 100 times higher than that calculated by SAI. If the Additive is conservatively assumed to contribute a maximum concentration of 0.09 ug/m^3 to airborne manganese levels, average daily manganese intake would increase from 3.3086 mg to 3.3104 mg. The contribution of the Additive to average daily intake of manganese would be only 0.054 percent. The degree of conservatism in this estimate is illustrated by the fact that average ambient manganese levels in Toronto, a major urban area where the Additive has been added to gasoline for over a decade at twice the concentration proposed by Ethyl in this proceeding, are well less than half the 0.09 ug/m3 maximum concentration.

proposed RDI for adults.[29/] Thus, there is no basis for concern that total manganese exposures associated with the Additive could contribute to either respiratory or neurological effects.[30/]

Dr. Fouts also makes the unsupported allegation that inhaled manganese from the Additive would have "greater bioavailability" than ingested manganese.[31/] There is absolutely no evidence that inhaled manganese and ingested manganese of the same chemical species act differently once absorbed into the body. For example, dissolution products of both ingested and inhaled

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[29/] The average newborn intake of manganese in food is approximately 0.0064 mg/day (see HAD at 3-89), or 100 times below the proposed RDI for infants. Newborn intake of manganese from air would have to be approximately 1000 times higher than that of adults to reach the infant RDI. There is, therefore, no reason to believe that the Additive would cause the average intake of manganese by newborns to exceed the RDI.

[30/] Dr. Fouts cites a World Health Organization (WHO) study (1980) to support the proposition that manganese "at far lower exposures contributes to the prevalence of pneumonia and bronchitis in the general population." Fouts Memorandum, Attachment at 1. All of the studies cited by the WHO, however, involved ambient manganese levels far in excess of those which would occur with widespread use of the Additive. One study, for example, showed an increase in pneumonia and bronchitis related to the operation of a ferro- and silico-manganese plant in Sauda, Norway. The airborne pollutants were extremely elevated with manganese levels at 45 ug/m3 and silica levels from 6.4-8.9 mg/m3. The WHO also cites studies from Japan and Italy, but no airborne exposure levels were reported in either of these studies. The final study cited by WHO involved the population of Dalmatia, Yugoslavia. The incidence of bronchitis in this final study did not appear to be dose related and the pneumonia incidence was not elevated. And, in any case, the WHO noted that confounding factors were not considered in the study. The "far lower exposures" referred to by Dr. Fouts, therefore, are about 1000 times greater than the average ambient manganese levels predicted to occur with use of the Additive. See Ethyl Comments, Appendix 2.

[31/] Fouts Memorandum, Attachment at 6.

manganese must enter the bloodstream and pass through the heart and lungs, and probably the kidney and the liver, before reaching the brain.[32/]

Moreover, while EPA's Health Assessment Document for Manganese indicates "[t]here are no quantitative data on absorption rates for inhaled manganese either in humans or animals,"[33/] one can make reasonable estimates of this absorption. Assuming that manganese deposited in the alveolar region of the lung is absorbed at a rate of 50-80 percent,[34/] the contribution of the Additive to the body burden of manganese is still only a tiny fraction of one percent of total manganese intake.

Finally, while the definitive knowledge of a dose/response relationship sought by Dr. Fouts would be useful in assessing the magnitude of the health risk at manganese exposure levels thought to affect health adversely, it would be pointless at the levels associated with use of the Additive. These levels are well within the RDIs for manganese. Thus, they fall within the range of biological need. Indeed, given the far larger contribution of food and water than air to manganese intake -- let alone the

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32/ Roth Report at D-2, Attachment D-1 at 1-2.

33/ See Roth Report, Attachment B-1 at 4-5.

34/ See R.B. Schlesinger, "Biological Disposition of Airborne Particles: Basic Principles and Application to Vehicular Emissions" in Air Pollution, the Automobile, and Public Health 247 (Watson, Bates & Kennedy eds. 1988) at 277. Since about 30 percent of the inhaled manganese particles would be deposited in the alvelor region of the lung, see supra note 26, this would mean that approximately 25 percent of inhaled manganese resulting from use of the Additive would be absorbed.

miniscule contribution of the Additive -- it would probably be impossible to design a cohort study with the power to detect changes in health associated with these trivial changes in exposure.[35/]

B. Susceptible Populations

Dr. Fouts suggests that certain populations (e.g., newborns, pregnant women, individuals with iron deficiency, idiopathic hemochromatosis, or biliary dysfunction) are more likely than the general population to experience adverse health effects from the manganese levels associated with use of the Additive.[36/] As noted by one independent health expert in Ethyl's July 23 comments, the World Health Organization has stated that an average annual concentration of manganese in ambient air of 1 ug/m^3 "should incorporate a sufficient margin of protection for the most sensitive population group."[37/] Even with use of the Additive, ambient manganese levels not otherwise affected by manganese emissions from point sources would remain at least an order of magnitude below that level.[38/]

[35/] Even if a cohort study were implemented, the absence of an observed effect after 20 years would not prove "conclusively" that low level manganese emissions do not adversely affect public health. The "conclusive" nature of the data sought by Dr. Fouts, therefore, cannot be obtained. Roth Letter at 7.

[36/] Fouts Memorandum, Attachment at 3, 11, 12, 13.

[37/] See Ethyl Comments, Appendix 7, Attachment 2 (emphasis added).

[38/] See Ethyl Comments, Appendix 2.

The Fouts Memorandum cites no evidence that any of the groups about which it expresses concern experience adverse effects from the level of manganese that will follow use of the Additive.[39/] Instead, it raises concerns based on evidence or

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[39/] The Fouts Memorandum cites a study by Collipp, et al. as support for its concern that accumulation of manganese by newborns contributes to later neurological effects. The Fouts Memorandum indicates that Collipp et al. associated manganese-enriched infant formulas with learning disability. In fact, Collipp et al. did not examine whether children fed high-manganese infant formula had a higher rate of learning disability. Instead, they compared hair manganese levels of learning disabled 7 to 10 year old children to those of normal children. They found that the learning disabled children had higher levels of manganese in their hair. In addition, they compared hair manganese levels of formula-fed and breast-fed infants to those of newborns. If, however, the hair manganese levels of four-month-old breast-fed and bottle-fed infants (the only age at which they presented data for both groups) are compared, there is no statistically significant difference. See Roth Letter at 7-9. Thus, this would seem an unlikely cause for later learning disability. In any case, no causal relationship was shown between manganese levels (whatever their source) and learning disability.

Moreover, enhanced uptake of manganese by newborns may fulfill a biological need. It has been suggested that "The higher retention [of manganese] in the premature infant may be the result of increased manganese absorption by the immature gut, immaturity of the excretory pathways for the element, and/or a higher requirement for manganese due to tissue synthesis and emergence of manganese enzymes." Hurley, L.S., Keen, C.L., "Manganese: Trace Elements in Human and Animal Nutrition," ed. W. Mertz, Vol. 1, 185-223 (1987). Even in infants that are not premature, elevated manganese levels may be necessary. Convulsive disorders in infants have been associated with low blood manganese levels. Dupont, C.L., Tanaka, Y., "Blood Manganese Levels in Children with Convulsive Disorders," Biochem. Med. Vol. 33 246-255 (1985). As Lonnerdal et al. (1987) point out:

> In contrast to other trace elements such as iron, zinc and copper, Mn stores are not thought to be accrued during fetal life; therefore, the infant may be dependant on an adequate supply of Mn during early

(continued...)

speculation that these populations experience enhanced manganese uptake or impaired manganese excretion.[40/] Since the contribution of the Additive to the total body burden of manganese will be vanishingly small, and since there is no evidence that these groups experience adverse health effects from exposure to present manganese levels,[41/] the concerns expressed in the Fouts Memorandum are baseless. As stated by Dr. W. Clark Cooper upon reviewing the Fouts Memorandum:

> If the [Fouts Memorandum] had concentrated on the importance of dose, it would have been much more informative. As stated on page 3, "Manganese is both a required nutrient and a toxic element depending on the route, duration and extent of manganese exposure, as well as the susceptibility of the person exposed." These factors are of course interrelated. There are differences in susceptibility for all chemicals, <u>but these are not important if we are dealing with exposures that are too low to harm even the most susceptible</u>.[42/]

[39/] (...continued)
postnatal life and consequently particularly susceptible to Mn deficiency . . . .

Lonnerdal, et al., "Manganese Uptake and Retention: Experimental Animal and Human Studies," Nutritional Bioavailability of Manganese, American Chemical Society, 9-20 (1987).

[40/] The existing evidence of enhanced manganese uptake apparently involves ingestion. Dr. Fouts cites <u>no evidence that enhanced uptake of inhaled manganese has ever been found in any population</u>.

[41/] Of note, <u>neither of the studies cited by Dr. Fouts regarding idiopathic hemochromatosis (Cartwright et al., 1979 and Whittaker et al., 1989) makes any reference to manganese</u>.

[42/] Letter from Dr. W. Clark Cooper to Dr. Donald Lynam dated August 17, 1990 (attachment 2 to these comments)[hereinafter "Cooper Letter"] at 1 (emphasis added).

C. Exposure to the Additive

The Fouts memorandum also alleges that dermal exposure to the Additive by the general population is a health concern. As Ethyl readily acknowledges, exposure to the Additive in its pure form can cause a variety of undesirable health effects.[43/] No adverse public health effect from dermal exposure to the Additive, however, can reasonably be anticipated at the concentrations proposed for the Additive in this proceeding.[44/]

One independent health expert, Dr. Cooper, points out that the Additive in unleaded gasoline as proposed by Ethyl in this proceeding would be extremely dilute (i.e., approximately one drop in a gallon of gasoline). As a result, use of the Additive "would not appreciably increase the risks associated with skin exposure to gasoline."[45/] As explained by Dr. Cooper,

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[43/] Waiver Application, Appendix 8 at 14.

[44/] Canada, for example, has evaluated the toxicity of the Additive, including its dermal toxicity, and permits the addition of the Additive to gasoline at concentrations twice as high as those proposed by Ethyl. See Ethyl Comments, Appendix 4.

[45/] Cooper Letter at 1. In addition to his concern regarding dermal exposure to the Additive, Dr. Fouts also suggests that the Additive may be "exhausted as a vapor containing MMT." Fouts Memorandum, Attachment at 7. This "possibility" cited by Dr. Fouts is not consistent with the available information concerning the Additive. In particular, Ethyl cited a study showing that the Additive was not detected in ambient air at several locations at street level in Toronto at a limit of detection of 0.00005 ug/m3 notwithstanding that the Additive was present in gasoline at twice the concentration proposed by Ethyl in this proceeding. See Waiver Application, Appendix 8 at 15, n. 26 and accompanying text. Dr. Fouts fails to address this study, much less provide any new information to cast doubt on its results. The "possibility" that the Additive is exhausted as a vapor is, therefore, baseless.

> Repeated or protracted exposure to gasoline should be avoided, whether or not it contains MMT. There are components, such as benzene, which are present in larger quantities, and which are more dangerous, than traces of MMT. I know of no problems reported in Canada relevant to this issue.[46/]

Dr. Cooper's conclusion is further confirmed by an analysis of the factors which govern dermal absorption. Whether and to what extent a gasoline component will be absorbed into the skin depends upon the concentration of the component, the duration of the exposure, and the affinity of the component for gasoline as opposed to water in terms of its solubility.[47/] Since (i) the concentration of the Additive in unleaded gasoline would be very low (approaching zero when compared to other components); (ii) the affinity of the Additive for gasoline is extremely high as opposed to its solubility in water;[48/] and (iii) the duration of any exposure to gasoline containing the Additive is likely to be very short, it is extremely unlikely that any realistic scenario for dermal contact with gasoline containing the Additive would lead to adverse health effects attributable to the Additive alone.

46/ Cooper Letter at 1.

47/ See "The Additive and Dermal Exposure," attached hereto as Attachment 3.

48/ The outer layer of skin contains between 10 to 70 percent water. See id.

IV. CONDUCTING A MASS BALANCE IS UNNECESSARY AND INAPPROPRIATE HERE.

In its waiver application, Ethyl reported the results of particulate testing conducted on eighteen of the vehicles used in Ethyl's 48 car test program. Using test procedures developed by EPA for the measurement of total particulate emissions from light-duty diesel vehicles, Ethyl reported that only about 0.5 percent of the manganese in the Additive is emitted from the tailpipe.[49/]

Since submittal of the waiver application, Ethyl has completed additional particulate testing on five more of the test vehicles under a range of driving conditions: 25 mph, 45 mph, and 60 mph. This testing used the same EPA test procedures noted above. The amount of manganese emitted from the tailpipe of these test cars ranged from as little as 1.5 percent of the manganese in the Additive at 45 mph, to no more than 6.9 percent at 60 mph. These test results, which are provided in Attachment 4, confirm the results of the earlier testing -- i.e., the amount of manganese emitted from cars using fuel containing the Additive will be extremely small.

Unaware of this more recent particulate testing or the conservative assumptions used by Ethyl to predict the effect of the Additive on environmental levels of manganese, Dr. Fouts

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49/ See Waiver Application, Appendix 3, at 15-16. Dr. Fouts mistakenly suggests that the initial particulate testing by Ethyl shows that 5 percent of the manganese in the Additive is emitted, rather than about 0.5 percent. See Fouts Memorandum, Attachment at 4.

suggests that "EPA should require that Ethyl conduct an appropriate mass balance to determine where the manganese has gone."[50/] As already noted by Ethyl, such an effort would be very problematic to perform and fraught with difficulty.[51/] The goal of such an analysis would be to account for an extremely small amount of material (only about 90 grams if all of the manganese in the Additive remained in the test vehicles) from at least 10,000 to 15,000 square centimeters of surface area on the internal parts of the automobile.[52/]

<u>There is no standardized method for conducting such an analysis</u>. It would require all of the parts of the automobile that might retain manganese from the Additive (e.g., the combustion chambers, pistons, spark plugs, manifolds, the catalyst, the exhaust pipe(s), the engine oil and filter) to be

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50/ <u>Id.</u> at 7. In particular, Dr. Fouts expresses concern that the manganese in the Additive, even if most of it remains in the vehicle, will be released to the environment "sooner or later." <u>Id.</u> at 4. As noted in previously filed comments, however, the amount of manganese typically present in an automobile dwarfs the very small amount of manganese present in the Additive, <u>even if all of the manganese in the Additive remains in the automobile after its useful life</u>. Over 100,000 miles, the amount of manganese consumed in the Additive is only about 120 grams. The steel used to make an automobile, by contrast, typically contains <u>seven to eight pounds of manganese</u>. <u>See</u> Letter to Public Docket from Dr. Francis Keenan, Director, Chemetals dated July 18, 1990 (docket entry IV-D-30). Moreover, in general, this steel is recycled. The small amount of manganese from the Additive would be indistinguishable from the other manganese in steel, and would become a part of the recycled steel.

51/ Ethyl Comments at 21, n. 46.

52/ The figure of 90 grams is derived as follows: (0.03125 grams manganese/gallon) X (75,000 miles/25 miles per gallon).

removed from the car, their coatings extracted and dissolved in acid, and the remaining solution analyzed for the presence of manganese.[53/] To gain access to these surface areas, various components of the automobiles would have to be disassembled either directly or by cutting them up. This aspect of the analysis alone would generate substantial uncertainties regarding ultimate results because of unavoidable losses of material in the removal process.

Faced with these uncertainties, and the fact that automobile emissions (not a mass balance) are the relevant issue in this proceeding, Ethyl based the high end of its environmental manganese level analyses on the conservative assumption that 30 percent of the manganese in the Additive would be emitted as airborne particulate.[54/] This assumption is conservative because it is based on particulate emission testing of older vehicles <u>without catalytic converters or other engine design changes</u>, such

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[53/] It would also require the analyst to be able to distinguish between manganese attributable to use of the Additive and the manganese otherwise present in the materials which make up the automobile. <u>See supra</u> note 51.

[54/] Dr. Fouts suggests, without reference to any supporting authority, that some of the manganese in the Additive might be emitted to the environment as vapor or very fine particles. Fouts Memorandum, Attachment at 6. Inasmuch as Ethyl has determined that the mass median equivalent diameter of the Mn_3O_4 particles emitted from the tailpipe of vehicles using the Additive is about 0.3 micrometers, Ethyl has already measured for the emission of "very fine" manganese particles. <u>See supra</u> note 26. Moreover, all of the studies which have examined the combustion products of the Additive have concluded that the principal product is <u>particles</u> of Mn_3O_4, not "manganese lost as vapor." <u>See</u> Ethyl Comments at 20, n. 45.

as electronic fuel injection and oxygen sensors, which have dramatically improved the fuel combustion efficiencies (and reduced particulate matter emissions) of automobiles.[55] This testing shows, for example, that total particulate emissions from cars not equipped with catalytic converters or contemporary fuel system components is more than 20 times higher than that reflected in Ethyl's particulate testing.[56]

Finally, Ethyl conducted an analysis relating the Additive's manganese emissions to emissions of lead from prior use of tetraethyl lead in gasoline, in order to add yet an additional level of conservatism to Ethyl's projections. Ethyl assumed that the effects of the Additive on environmental levels of manganese would be essentially the same as those associated with use of

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[55] See Ethyl Comments at 21, n. 46.

[56] See Habib, et al., "Characterization and Control of Gaseous and Particulate Exhaust Emissions from Vehicles," Air Pollution Control Assoc., Fifth Technical Meeting (October 1970). Dr. Fouts cites a study by Davis et al. (1988) to support the proposition that use of the Additive will increase environmental levels of manganese. See Fouts Memorandum, Attachment at 6. Ethyl does not dispute this general proposition. The important point, not recognized by Dr. Fouts, is that even when one applies very conservative assumptions about the amount of manganese emitted from vehicles using fuel containing the Additive, the resulting impact on average environmental manganese levels is very small. Indeed, accepting the Davis study at face value, it shows only that use of the Additive at a much higher concentration in gasoline (0.1 grams per gallon), and in older cars not equipped with catalytic converters or other automotive engineering improvements, did not increase ambient manganese levels in California above the range normally found elsewhere in the country. See Ethyl Comments, at 24, n. 52.

lead over the course of 50 years, expressed as a simple ratio of the relative lead and manganese concentrations in gasoline.[57/]

This analysis does not depend upon knowledge of the exact percentage of either manganese or lead emitted. Rather, the model assumes only that similar percentages are emitted. For example, if the automotive contribution to lead in the environment can be attributed to the fact that 30 percent of the lead in gasoline was emitted, then the predicted automotive contribution of manganese in the environment would also be attributable to the emission of 30 percent of the manganese in the Additive.

For vehicles using leaded fuel, studies of particulate emissions suggest that as much as 75 percent of the lead used in gasoline was emitted to the environment (35 percent to the ambient air and 40 percent to the soil based on particle size).[58/] Application of this model, therefore, enables one to predict the effects of the Additive on environmental levels of manganese <u>even if up to 75 percent of the manganese in the fuel is emitted to the environment</u>.

Using these conservative assumptions, Ethyl calculated the following "worst-case" predictions regarding the Additive's

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[57/] <u>See</u> Ethyl Comments, Appendix 2, Attachment 2.

[58/] Ter Haar et al., "Composition, Size and Control of Automotive Exhaust Particulates," Jour. of the Air Poll. Control Assoc., Volume 22, 39-46 (1972).

impact on environmental levels of manganese. The actual impacts would likely be substantially less than listed below.

1. Ambient Airborne Manganese Levels -- An increase of 0.017 ug/m3.

2. Manganese Soil Levels -- An increase of only 12 ppm in the average manganese in soil level (about 1000 ppm) after 50 years of use one meter from a busy expressway, decreasing to background within 15 meters.[59]

Inasmuch as independent health experts have concluded that use of the Additive would not adversely affect public health even at levels much higher than these "worst-case" predictions,[60] there is no need to conduct a mass balance. Given the uncertainties associated with such an effort, it would not likely provide -- even in the best of circumstances -- information on the basis of which more significant environmental impacts would be predicted.[61]

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[59] This predicted increase ignores the fact that manganese is soluble in soil with the result that the predicted "worst-case" concentration is "overstated." See Ethyl Comments at 27-28.

[60] Roth Associates concludes that even if the Additive caused an increase in ambient manganese levels of 0.09 ug/m3 -- a level more than four times higher than the highest worst case impact reported by Ethyl -- the Additive would not adversely affect public health. Roth Report, at A-1, F-1 to F-2. Dr. Lauwerys concludes that so long as ambient manganese levels remain below 1 ug/m3 even the health of the most sensitive populations will not be adversely affected. Ethyl Comments, Appendix 7, at Attachment 2.

[61] In its comments, Ford asserts that 24 percent of the Mn3O4 formed from use of the Additive is deposited in the catalyst alone, to say nothing of the rest of vehicle components. See Ford Motor Company Comments (docket entry III-D-59) at 5. It is, therefore, totally unrealistic to assume that any more than 75

(continued...)

IV. CONCLUSION

Ethyl's estimates of environmental manganese levels if the Additive is used at the concentration proposed in its application are well-documented and conservative. At that concentration, the Additive will have an infinitesimal effect on human manganese exposure. Expected levels of manganese intake will remain a tiny fraction of one percent of the FDA's proposed Reference Daily Intakes -- a level that reflects those manganese levels necessary for the body to function properly. Similarly, dermal exposure to the Additive as a result of Ethyl's proposed use of the Additive presents no threat to exposed individuals. Therefore, given the reduction in other pollutants of clear health concern that result from use of the Additive,[62/] granting Ethyl's application for a § 211(f) waiver can be expected to enhance, not endanger, public health.

[61/] (...continued)
percent of the manganese in the Additive is emitted to the environment. In the unlikely event that a mass balance showed that 75 percent of the manganese in the Additive was emitted to the environment, the "worst-case" environmental impacts predicted by Ethyl -- impacts that entail no public health concern -- would not change. See supra note 58 and accompanying text.

[62/] See Roth Report at E-1 to E-5.

ATTACHMENT 1

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August 23, 1990

Dr. Donald R. Lynam
Director, Air Conservation and Industrial Hygiene
Ethyl Corporation
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Dear Dr. Lynam:

In a memorandum to the EPA administrator on June 7, 1990, the Director of the National Institute of Environmental Health Sciences (NIEHS) raised some important concerns about the use of MMT as a fuel additive. In an earlier report we responded to these concerns and other issues raised in testimony before the Environmental Protection Agency (EPA). Since we submitted our response to the EPA docket, NIEHS has raised additional concerns. We have examined these concerns with the assistance of Dr. Carl Schulz, who was a major contributor to our earlier report. In our response to recent NIEHS comments we will focus on the following questions:

1. Do low levels of manganese contribute to respiratory effects?

2. Does manganese promote neurological disease at doses lower than those that produce overt signs and symptoms?

3. Is manganese associated with learning disabilities in children?

4. Do infants absorb manganese more readily than adults?

5. Is Mn_3O_4 more toxic than other forms of manganese?

1. RESPIRATORY EFFECTS OF MANGANESE

High levels of manganese (400 $\mu g/m^3$ - 16,000 $\mu g/m^3$) have been associated with increased rates of respiratory disease in occupational settings, and increased rates of pneumonia have been found in communities living near ferromanganese plants (exposed to >30 $\mu g/m^3$). As we noted in our previous report, lower levels of manganese (3-11 $\mu g/m^3$) have reportedly been associated with respiratory symptoms in a study by Nogawa et al. (1977). This study is seriously flawed, and was not considered reliable by either the EPA or the Health Effects Institute. One of the most serious problems with the Nogawa et al. study is the lack of reliable exposure data.

The amount of manganese which would be added to the ambient air from MMT use is 0.0009 $\mu g/m^3$, which would not significantly increase the current average level of 0.03 $\mu g/m^3$. Conservatively assuming a contribution from MMT of 0.09 $\mu g/m^3$ would increase the ambient manganese level to 0.12 $\mu g/m^3$, which is still 25 times lower than even the lowest level of manganese suggested by the Nogawa et al. study. The Kimbrough et al. (1989) article cited by NIEHS adds no information on respiratory effects, since it is only a listing of chemicals and not a research paper.

2. NEUROLOGICAL EFFECTS OF MANGANESE

NIEHS expressed concern that exposure to low doses of manganese may cause "silent" neurological damage. On page 2 of their memorandum NIEHS states that "Given the extent of cell damage and neurotransmitter depletion necessary prior to the onset of overt disease, manganese can produce substantial damage to the extrapyramidal tract prior to the observation of signs and symptoms of clinical disease." There are several reasons to reject this hypothesis in the case of manganese from MMT use: (1) The resulting level of manganese in the ambient air would be far below the lowest observable effects level (LOEL) found from the epidemiological data; (2) It has never been established that manganese neurotoxicity is a result of dopamine depletion; (3) The amount of manganese which would be added to the ambient air is small compared to current levels; (4) Manganese is an essential nutrient; and (5) Manganese intake from inhalation rarely constitutes more than 1% of the total daily intake of manganese, and the contribution of MMT to daily manganese intake would be a small fraction of 1 percent.

Epidemiological Data: There have been studies reporting a lack of effect after moderate exposure (.17 $\mu g/m^3$ - 2.3 mg/m^3) to manganese [Sabnis (1966); Saric et al. (1975)]. In its 1984 Health Assessment Document, the EPA found that "The human studies are not adequate to identify a dose-response relationship, but do permit the identification of the LOEL." They found that Saric et al. (1977) and Chandra et al. (1981) "suggest that the LOEL may range as low as 0.3 mg/m^3 (300 $\mu g/m^3$)." Thus, it is far-fetched to believe that there would be neurological effects below 100 $\mu g/m^3$, which is lower than even suggested by Saric et al. (1977). Considering that the quantity of manganese which would be added to the ambient air by MMT use is at least 10,000 times lower than this, there is more than adequate evidence that MMT use in gasoline will not contribute to neurological effects.

Ethyl Corporation has indicated that MMT use would lead to an expected increase in ambient manganese levels of 0.0009 $\mu g/m^3$. Compared to the current average ambient concentration of 0.03 $\mu g/m^3$, this would be negligible. In our earlier report, we also considered a conservative increase of 0.09 $\mu g/m^3$ from MMT use. Even then, the resulting ambient manganese concentration would be 0.12 $\mu g/m^3$, which is 2,500 times lower than the LOEL cited by the EPA.

NIEHS cited three studies which have reported neurological signs and symptoms without full parkinsonian syndrome: Ferraz et al. (1988), Sano et al. (1982), and Szeliga-Cetnarska (1987).

Ferraz et al. (1988) reported two cases of parkinsonism in two agricultural workers exposed to the fungicide maneb (manganese ethylene-bis-dithiocarbamate). A study of workers exposed to maneb showed a significant increase in headaches, nervousness, fatigue, memory complaints, sleepiness, and rigidity as compared to a control group. The mean blood manganese content did not differ significantly between the exposed and nonexposed groups, and did not differ between groups with and without neurologic symptoms.

No data is given to indicate the level of exposure to manganese; however, the authors stated that 84% of the exposed individuals did not use the fungicide in accordance with the manufacturer's recommendations (i.e., using mask and gloves, and according to the wind direction). The authors hypothesized that the hazard of maneb is probably due to manganese potentiated by the organic fraction of maneb. Thus, manganese is not clearly implicated in this study.

Sano et al. (1982, English abstract only, full text in Japanese) found increased neurological symptoms among a group of manganese mine workers and ore grinders as compared to a control group. The authors stated that most of the exposed group had been employed in small industrial factories with less than five employees under very poor working conditions. The incidence of symptoms increased with the period of exposure to manganese, and many patients reported symptoms more than five years after retiring. The manganese levels in Sano et al. are not clear, but since the subjects worked mining and grinding manganese ore, in all likelihood manganese levels were many orders of magnitude higher than would be associated with MMT use.

Szeliga-Cetnarska (1987, English abstract only, full text in Polish) carried out electrophysiological tests on 57 flux division workers exposed to manganese dioxide, and a control group of 22 subjects with no occupational exposure to toxic substances. The investigators found reduced conduction in motor fibers of 23 flux workers, and in sensory fibers in 23 subjects. The electromyogram showed concurrent denervation with changed motor conduction in 21 subjects.

Again, no exposure data are given in this case. It is clear that this study discusses occupational exposure to manganese, but it is not clear if the workers were exposed to other toxic substances. It is also unclear how the control group was chosen.

All three of the studies cited by NIEHS involve occupational exposure to unknown quantities of manganese. Sano et al. (1982) and Szeliga-Cetnarska (1987) provide little more than speculation, since only the abstracts are available in English. Ferraz et al. (1985) provides information on a new possible source of manganese intoxication; however, it is not relevant to a discussion of manganese exposure from MMT, due to the other organic compounds present in the fungicide and the high exposure levels. The studies cited by NIEHS provide no evidence of health effects from low level exposure to manganese, since the levels are not given, and they are most likely high. Thus we conclude, as in our earlier report, that the public health will not be adversely affected by increased manganese from MMT use.

Mechanism of Neurotoxicity: NIEHS argues that manganese can cause "silent" neurological changes at doses lower than those that produce overt signs of intoxication and that these changes could contribute to the premature onset of unspecified neurologic disease. This hypothesis, which has been developed by John Donaldson (Donaldson, 1987), is unsupported by experimental evidence. Furthermore, since the incremental exposures to manganese that might be associated with the use of MMT in gasoline are small compared to normal environmental exposures to manganese in the diet, this hypothesis requires one to conclude that even though manganese is a required nutrient, normal homeostatic mechanisms that control manganese levels in the body do not prevent gradual neurological damage from such exposures.

NIEHS cited Archibald and Tyree (1987) as the basis for the assertion that "damage to approximately 80% of the cells and a reduction of the neurotransmitter levels to under 20% of their typical concentration is necessary before clinical signs and symptoms of Parkinson's Disease are identified." The study by Archibald and Tyree (1987) provided no evidence for this assertion since it was a study of the effect of manganese upon dopamine oxidation in vitro. The quote used by NIEHS is actually found in the introduction of Archibald and Tyree (1987) and was referenced to a series of review articles authored by Donaldson, Barbeau, and Cotzias. Interestingly, the assertion was preceded by the statement that "Parkinson's disease is believed to be caused in large measure by a reduction in the levels of the catecholamine neurotransmitter dopamine in the caudate nucleus." The use of the word "believed" in this statement attests to the hypothetical nature of the statement.

NIEHS also cited a review by Jellinger (1987) as indicating that in Parkinson's disease the loss of pigmented nigral neurons ranged from 63% to 84%. While this may be true, it has no obvious relevance to the issue of manganese toxicity because

Parkinson's disease is clinically and pathologically distinct from manganese intoxication. Bleecker (1988) pointed out the clinical and neuropathological differences between Parkinson's disease and manganese toxicity and concluded that manganese toxicity affects primarily the cells of the striatum and globus pallidus which are not dopaminergic.

The uncertainty surrounding the pathogenesis of manganese neurotoxicity has recently been highlighted by the experiments of Eriksson et al. (1987). These authors treated male macaque monkeys with repeated subcutaneous injections of MnO_2 (8 grams over 5 months) resulting in numerous signs of manganese neurotoxicity. They noted a severe loss of neuronal cells in the globus pallidus while the rest of the brain appeared normal. They noted that these results were not consistent with the reported findings of Gupta et al. (1980) who reported the loss of pigmented neurons in the substantia nigra. The results of Eriksson et al. are consistent with the conclusion of Bleecker (1988) that manganese poisoning differs from Parkinson's disease in that the former affects the globus pallidus while the latter involves the substantia nigra.

Finally, the results of a study by Neff et al. (1969) appear to directly refute the basic premise that severe neuronal damage may occur without any outward manifestation of manganese toxicity. These authors concluded that "it is important to recognize that clinical and biochemical abnormalities may appear before histopathological changes in brain can be demonstrated, and that the presence of histological changes in specific locations may not explain the clinical manifestations."

In conclusion, the mechanism and pathogenesis of manganese neurotoxicity in humans and primates have not been established, and controversy remains regarding the precise areas of the brain that are affected and the similarities and differences between manganese toxicity and idiopathic neuronal disorders associated with old age. There is little experimental evidence available in support of the hypothesis that exposure to manganese at concentrations below those that cause overt signs and symptoms of neurological disease damages neurons or potentiates other neuronal disorders. One study even provides evidence that the opposite is true.

Contribution of Inhaled Manganese to Daily Intake: It is important to recognize that inhaled manganese contributes very little (less than 1%) to the total daily intake of manganese (see Attachment B). Assuming an ambient manganese concentration of 0.03 $\mu g/m^3$ and an adult ventilation rate of 20 m^3/day, we find that inhalation contributes only 0.6 μg/day (0.0006 mg/day). The average manganese intake for an adult is approximately 3.31 mg; thus inhaled manganese contributes only .018 percent of the total manganese intake.

The addition of 0.0009 $\mu g/m^3$ manganese to the ambient air would contribute 0.018 μg/day (0.000018 mg/day) to the total manganese intake, which represents a 0.0005 percent increase in total intake. The addition of 0.09 $\mu g/m^3$ of manganese to the ambient air represents an increase of 0.0544 percent (see Attachment B). Considering that manganese is an essential nutrient, such a minor increase in daily intake cannot be considered a health threat.

Summary: The nature of the scientific process makes it impossible to prove that neurological changes do not occur after chronic exposure to low levels of manganese; however, there is sufficient epidemiological data to conclude that there would be no neurological effects below 100 $\mu g/m^3$. The assertion by NIEHS that low levels of manganese may cause "silent" neurological damage is not based on sound scientific evidence. The increases in ambient manganese levels which would result from MMT use are small, and are far below levels which would be of concern.

3. LEARNING DISABILITIES AND MANGANESE RETENTION

NIEHS suggests on page 3 of their memorandum that manganese retention is higher in infants and young children than in adults. They also state that use of manganese-enriched infant formula has been associated with learning disabilities in children. This finding is based on a 1983 study by Collipp et al.

Collipp et al. (1983) is a two-part study designed to investigate a possible correlation between high manganese levels in hair and hyperactivity in children. The first part of the study involved determining the hair manganese levels of infants and children from birth to 8 years old who were formula-fed and breast-fed. The second part of the study compared hair manganese levels in hyperactive and normal children aged 7 to 10 years old.

The results of part 1 are summarized in Table II of the study. The table shows that at birth the mean hair manganese level in infants was 0.19 $\mu g/m^3$. The hair manganese levels for formula-fed infants increased to 0.965 $\mu g/m^3$ after 6 weeks, to 0.685 $\mu g/m^3$ after 4 months, to 0.587 $\mu g/m^3$ after 9 months, and to 0.398 $\mu g/m^3$ after 3 years. The hair manganese levels for breast-fed infants was 0.330 $\mu g/m^3$ after 4 months.

The authors performed statistical hypothesis tests and concluded that the hair manganese levels for formula-fed infants, at all ages measured, differed significantly from the hair manganese levels of infants. They also found that the hair manganese levels for breast-fed infants did not differ significantly from those of newborns. They attributed these differences to the higher concentration of manganese in formula as compared to mother's milk.

There are major problems with the conclusions drawn from part 1 of the study. Instead of comparing the mean hair manganese levels for formula-fed infants and newborns, it is of more interest to compare the formula-fed infants to the breast-fed infants. In fact, the mean values for formula-fed and breast-fed infants did not differ significantly at 4 months of age. Further complicating the picture is the fact that the age of the infants in the breast-fed group ranged from 2 months to 24 months, although they were considered in one group. As is illustrated by the different groups of formula-fed infants, manganese levels can vary considerably over this wide an age range.

The data presented in Collipp et al. (1983) seem to show that for formula-fed infants, manganese levels in hair increase greatly at 6 weeks and then fall gradually, even while still being fed formula. It seems likely that breast-fed infants would follow a similar pattern, although this study provides no evidence either way. The authors seem to be assuming that the hair manganese levels in breast-fed infants do not change throughout their infancy.

The use of hair samples to measure manganese in the body makes the results of this study even more difficult to interpret. Even if it is true that manganese levels in the hair of formula-fed infants are higher than for breast-fed infants, it is not clear what this says about the body burden of manganese. In a study of manganese exposed aborigines on Groote Eylandt, Australia, Stauber and Florence (1989) found that manganese in the hair was largely due to exogenous sources, and did not distinguish between those persons affected and unaffected by neurological symptoms.

In the second part of the Collipp et al. study, the authors found that the hair manganese levels for a group of hyperactive, learning disabled children (aged 7-10 years) were higher than for normal children. This finding is similar to that of two earlier studies, Barlow and Kapel (1979), and Pihl and Parkes (1977). Both of these studies measured multiple trace elements. Barlow and Kapel found that only manganese was significantly elevated, but Pihl and Parkes found that learning disabled children had significantly elevated levels of manganese, sodium, cadmium, and chromium, and reduced levels of cobalt, copper, and lithium.

These findings suggest that indeed there may be chemical imbalances in learning disabled children, and in particular that there are imbalances in manganese. However, to conclude that there is an association between manganese-enriched infant formula and learning disabilities, as the authors seem to conclude, is not warranted from these data. The authors provide no evidence that there is a higher incidence of learning disabilities among formula-fed infants, nor do they provide any evidence that ingestion of manganese in any way contributes to learning disabilities. Moreover, none of the material discussed by the authors involves inhalation, and given the far smaller contribution of inhalation to total manganese, there is no reason to believe that inhaled manganese should be a concern.

4. ABSORPTION OF MANGANESE IN INFANTS

NIEHS cites several studies of the uptake of manganese from the gastrointestinal tract in neonatal rodents as the basis for an argument that human infants "do not have the capability of limiting gastrointestinal absorption and excretion to the same extent as do adults." For reasons that are not entirely clear, NIEHS believes that this may predispose to the development of neurological disease later in life. There are several flaws in this argument. In the first place, rats and mice are not humans and the use of data from rodent studies to predict what might happen in human infants is not scientifically supportable. In the introduction to their paper, Rehnberg et al. (1980) state, "In the rat, these barriers (to the uptake of particulate Mn) are not established until weaning... Furthermore, Fe deficiency, which is the normal condition of preweaning rats, has been shown to increase the absorption of Mn,... The gastrointestinal tract of human infants is relatively mature compared to that of neonatal rats." Cahill et al. (1980) also noted in their discussion that "(c)ompared to human infants, the rodent gastrointestinal tract is relatively immature at birth."

Second, NIEHS relied upon studies in which exposure levels are high to predict what might happen at exposures that are expected to be only a small increment of normal ambient exposures. The doses of Mn administered to neonatal rodents ranged from 25 μg/day (King et al. 1975, Cahill et al. 1980) to 12,000 μg/day (Rehnberg et al. 1980). WHO (1981) estimated that breast-fed human infants are exposed to 2 to 4 μg/kg per day for the first few months of life.

Third, NIEHS implies that excessive absorption of manganese during infancy will result in permanently elevated levels of manganese in the brain and irreversible damage to neurons. There is no evidence for either of these assumptions. The results of Cahill et al. (1980) indicated that the retention of Mn in the brain was independent of the age at which the manganese was administered to neonatal rats. In other words, even though uptake was greater during the early prenatal period, normal excretory mechanisms served to reduce manganese levels in the brain later in life. While no such experiments have been performed, it is to be expected that normal homeostatic mechanisms which control the excretion as well as the absorption of manganese would result in similar body burdens shortly after weaning in young rats neonatally exposed to high levels of manganese and in those exposed to normal levels of manganese.

Finally, NIEHS ignores the evidence that human infants may be on the borderline of manganese deficiency during the early neonatal period. WHO (1981) reported that breast milk contains very low concentrations of manganese, and nursing infants exhibit a distinctly negative manganese balance during the first week of life. WHO cited both Widdowson (1969) and Schroeder et al. (1966) as showing that manganese tissue levels decreased during the early neonatal period. Miller et al. (1975) noted that the avid accumulation of manganese by neonatal mice is necessary because of the small concentration of this essential micronutrient in mouse milk. Thus, even if manganese absorption is enhanced in very young human infants (unestablished), this may be beneficial by preventing a deficiency of this essential element.

5. RELATIVE TOXICITY OF Mn_3O_4

Ter Haar et al. (1975) reported that Mn_3O_4 was the predominant chemical form of manganese in the exhaust from internal combustion engines burning gasoline to which MMT has been added. In their memorandum, NIEHS raised the issue of whether Mn_3O_4 may be more toxic than other forms of manganese. While definitive data are not available at this time, the evidence does not suggest Mn_3O_4 is more toxic than other Mn compounds. The limited data that are available suggest that any differences in toxicity among various inorganic manganese compounds are likely to be quantitative rather than qualitative and are likely to be small. This generalization is particularly valid for the various oxides of manganese which are the forms to which humans are most likely to be exposed in ambient air. (WHO 1981).

The acute lethal toxicity of a number of manganese compounds, not including Mn_3O_4, were compiled by WHO (1981). The WHO Task Group concluded that the toxicity of manganese is somewhat dependent on chemical form, with divalent manganese being 2.5-3 times more toxic than the trivalent form. Mn_3O_4 is a mixture of manganese valence states with one of the manganese atoms being divalent and two, trivalent.

Gianutsos et al. (1985) measured the manganese content of the blood and brains of mice given single subcutaneous injections of three different forms of manganese, $MnCl_2$, Mn_3O_4, or MMT. Increased manganese levels in the blood and brain were observed after administration of each of the compounds. Higher brain levels occurred after administration of $MnCl_2$ than after administration of either Mn_3O_4 or MMT. $MnCL_2$ is water-soluble, whereas Mn_3O_4 and MMT are not. Drown et al. (1986) also showed differences in the disposition of manganese that were related to solubility. They measured tissue levels of manganese after intratracheal instillation of either $MnCl_2$ or Mn_3O_4 in rats. $MnCl_2$ was cleared from the lungs and was taken up by the brain more rapidly than Mn_3O_4. However, both compounds remained in the brain at high levels for several weeks. Taken together, the studies of Gianutsos et al. and Drown et al. suggest that the uptake and disposition of manganese compounds may be determined, in part, by their water solubility with soluble compounds being more bioavailable.

The acute lethal toxicity of manganese compounds as determined in mice, rats, and guinea pigs may have little relevance to the induction of chronic manganese intoxication in humans. The administration of manganese compounds to rodents fails to cause the characteristic chronic manganese intoxication that is seen in primates (WHO 1981). Morganti et al. (1985) exposed male Swiss Webster mice to MnO_2 for 32 weeks and observed no histopathological changes or grossly visible signs of neurotoxicity such as those seen in monkeys or humans.

Primate studies are more relevant in determining the relative toxicity of manganese in humans. Comparative studies of manganese compounds have not been performed in primates, but Ulrich et al. (1979a,b) exposed both rats and monkeys to an aerosol of Mn_3O_4 produced by the combustion of MMT for 9 months. No alterations of pulmonary function and no grossly visible signs of neurotoxicity were seen in either species even at the highest exposure level of 1,152 $\mu g/m^3$. This study provides additional evidence that it is difficult to produce chronic manganese intoxication in experimental animals.

Eriksson et al. (1987) were able to produce in monkeys a condition resembling chronic manganese intoxication in humans by administering subcutaneous injections of MnO_2 over a five-month period for a total dose of 8 grams of manganese. The monkeys became hypoactive and had an unsteady gait and tremor. Histopathologic examination of brains from treated monkeys revealed severe neuronal cell loss in the globus pallidus.

Several authors have investigated the mechanism by which manganese may produce neurotoxicity in vitro. These authors have hypothesized that the characteristic pathology requires the presence of manganese in the +3 oxidation state which then destroys catecholamines (Donaldson 1987; Archibald and Tyree 1987). While this hypothetical mechanism implies that higher oxidation states of manganese may be more toxic than the +2 state, there is little in vivo evidence to support the hypothesis, and almost nothing is known about the conversion of manganese from one oxidation state to another once it is absorbed.

In conclusion, the question of whether or not Mn_3O_4 is more or less toxic than other forms of manganese cannot be answered definitively at the present time. There is no reliable evidence that Mn_3O_4 is more toxic than other forms of manganese, nor is there evidence that human infants absorb and retain Mn_3O_4 more readily than other forms of manganese.

Sincerely,

H. Daniel Roth

H. Daniel Roth

Philip A. Walker

Philip A. Walker

ATTACHMENT A

MANGANESE EPIDEMIOLOGY

Author	*(Year)*	*Population Studied*	*Health Effects Observed*	*Exposure Levels*	*Comments*
Baader	(1932)	Pyrolusite mill workers	Toxic effects on lung; pneumonia	N/A	
Elstad	(1939a,b)	People living near a ferro- and silicomanganese plant in Sauda, Norway	Labor pneumonia	30 - 64 $\mu g/m^3$	Also exposed to silica at 6.4 - 8.9 mg/m^3
Flinn et al.	(1940)	Manganese ore crushing mill workers	Manganese poisoning	≤173 $\mu g/m^3$	No cases among 9 workers with exposures ≤30 $\mu g/m^3$
Flinn et al.	(1941)	Manganese ore crushing mill workers	Manganism	10 - 30 mg/m^3 30 - 180 mg/m^3	No manganism at low exposures; 4.4% at high exposures.
Ansola et al.	(1944)	Manganese miners	Manganese poisoning	62.5 - 250 mg/m^3	Onset of disease possible within a few months with high exposures.
Davies	(1946)	Potassium Permanganate workers	Pneumonia	.1 - 13.7 mg/m^3 80% of particles were smaller than 0.2 μm.	No case of chronic manganese poisoning over 8 years.

Author (Year)	*Population Studied*	*Health Effects Observed*	*Exposure Levels*	*Comments*
Davies and Harding (1949)	Potassium Permanganate workers	Pneumonia	.1 - 13.7 mg/m^3	Follow-up of Davies (1946).
Rodier (1955)	Miners in Morocco	Manganese poisoning	250 - 450 mg/m^3	Onset of disease possible within a few months with high exposures; individual susceptibility shown.
Schuler et al. (1957)	Miners	Manganism	1.5 - 16 mg/m^3	Manganese oxides studied.
Horiguchi (1966)	Crushing & refining workers; dry-cell & welding rod manufacturers	Neurological/central nervous system effects	2.3 - 17.1 mg/m^3 1.9 - 21.1 mg/m^3 3.8 - 8.1 mg/m^3	Correlation found between neurological findings and manganese urine levels.
Sabnis et al. (1966)	Ferromanganese plant workers	Manganese poisoning	Weighted avg. $\leq$2.3 mg/m^3	No cases or symptoms; 1000 workers studied.
Whitlock et al. (1966)	Ferromanganese plant workers	Chronic manganese poisoning	.1 - 4.7 mg/m^3	
Mandzgaladze (1967)	Wives of manganese processing plant workers	Spontaneous abortions and stillbirths	N/A	Higher rates among cases vs. controls for both problems; wives' occupations not taken into account.

Author	*(Year)*	*Population Studied*	*Health Effects Observed*	*Exposure Levels*	*Comments*
Tanaka and Lieben	(1969)	Industrial workers	Manganism	<5 mg/m^3 5 - 30 mg/m^3	No manganism at low exposures; 6% at high exposures.
Horiuchi	(1970)	Crushing & refining workers; dry-cell & welding rod manufacturers	Neurological/central nervous system effects	2.3 - 17.1 mg/m^3 1.9 - 21.1 mg/m^3 3.8 - 8.1 mg/m^3	Correlation found between neurological findings and manganese urine levels.
Suzuki	(1970)	Ferromanganese plant workers	Pneumonia	N/A	Pneumonia rates twice those of other area plant workers.
Emara et al.	(1971)	Dry-cell battery workers	Manganese poisoning/ psychosis	6.8 - 42.2 mg/m^3	
Kagamimori et al.	(1973)	Students in same schools as Nogawa	Improved respiratory conditions after Mn levels were reduced	Not reported; lower than for Nogawa (1973)	Shortcomings similar to Nogawa (1973).
Nogawa et al.	(1973)	Children in school near ferromanganese plant	Respiratory symptoms	3 - 11 $\mu g/m^3$	Not reliable, serious problems.

Author	*(Year)*	*Population Studied*	*Health Effects Observed*	*Exposure Levels*	*Comments*
Smyth et al.	(1973)	Miners	Manganese poisoning	2.1 - 12.9 mg/m^3	Individual susceptibility shown.
Suzuki et al.	(1973a,b)	Ferromanganese factory workers	Multiple symptoms	4.9 mg/m^3 1 - 2 mg/m^3	Symptoms increased with length of employment.
Saric et al.	(1974)	Manganese alloy production workers	Chronic lung disease	.39 - 16.35 mg/m^3	
Saric et al.	(1975)	Population in Yugoslavia living near a manganese alloy plant	Pneumonia, bronchitis, peribronchitis	.17 - .44 $\mu g/m^3$	Incidence of pneumonia did not exceed expected values.
Saric et al.	(1977)	Manganese alloy production workers	Neurological symptoms	.39 - 16.35 mg/m^3	Same workers as in Saric et al. (1974)
Saric et al.	(1977)	Ferroalloy and electrode plant workers; aluminum workers	Neurotoxic effects	300 - 5,000 $\mu g/m^3$	Serious shortcomings. See comments in text of our letter.
Saric et al.	(1978)	Population in Yugoslavia living near a manganese alloy plant	Pneumonia, bronchitis, peribronchitis	.17 - .44 $\mu g/m^3$	Incidence of pneumonia did not exceed expected values.

Author	(Year)	Population Studied	Health Effects Observed	Exposure Levels	Comments
Chandra et al.	(1981)	Welders	Neurological symptoms	.5 - 2.6 mg/m^3	Three exposure groups.
Sano et al.	(1982)	Retired miners & ore grinders in Japan	Neurological effects		See comments in text of our letter.
Roels et al.	(1987)	Manganese-exposed workers	Preclinical intoxication signs	$\approx$1,000 $\mu g/m^3$	
Szeliga-Cetnarska	(1987)	Workers exposed to MnO_2	Diminished peripheral nerve conduction rate	N/A	See comments in text of our letter.
Ferraz et al.	(1988)	Agricultural workers exposed to a manganese fungicide	Parkinsonian syndrome	N/A	See comments in text of our letter.
Hams and Fabri	(1988)	Australian aborigines living near manganese ore deposits	Neurological disorders	N/A	
Cawte et al.	(1989)	Several manganese-exposed populations	Motor neuron disease	N/A	Review article.
Wang et al. (1989) Huang et al. (1989)		Ferromanganese smelter workers	Manganese-induced parkinsonism	>28.8 mg/m^3	

Author (Year)	*Population Studied*	*Health Effects Observed*	*Exposure Levels*	*Comments*
Stauber (1989) and Florence	Australian aborigines living near manganese ore deposits	Neurological effects	N/A	No relation between manganese levels in hair and neurological problems.
Gottschalk et al. (undated)	California prison inmates	Violent behavior	N/A	Seriously flawed.

ATTACHMENT B

TOTAL DAILY MANGANESE INTAKE
(In milligrams)

Adult Exposure	Food	Air	Water	Total	Added Mn from MMT use	Manganese Increase (Average)	Manganese Increase (High)
Average intake	3.3	0.0006	0.008	3.31	0.000018	0.0005%	0.0544%
High intake*	5.5	0.2000	1.994	7.69	0.001800	0.0002%	0.0234%

* High intake of manganese from food is based on the highest average reported in Tipton et al. (1969); Air intake is based on concentrations measured near sites of manganese alloy manufacturing; Water intake is based on the 99th percentile of concentrations in private wells.

Source of Data: EPA Health Assessment Document for Manganese, 1984

ATTACHMENT 2

W. CLARK COOPER, M.D.
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LAFAYETTE, CALIFORNIA 94549
PHONE (415) 284-5850

August 17, 1990

Donald R. Lynam Ph.D.
Director, Air Conservation & Industrial Hygiene
Ethyl Corporation
451 Florida Street
Baton Rouge, LA 70801

Dear Dr. Lynam:

I have reviewed, insofar as time permitted, the July 23rd statement of the National Institute of Environmental Health Sciences regarding possible health hazards from the use of MMT as a gasoline additive. I found nothing in it, nor in the accompanying documentation, that altered my opinion that there is no scientifically acceptable evidence to justify banning the use of MMT

I don't have time to discuss in detail each section of the NIEHS statement. Much of it is irrelevant to the basic issue, i.e. do very small amounts of inorganic manganese added to the environment, within the range necessary for human health, under some circumstances cause harmful effects on health? If the NIEHS statement had concentrated on the importance of dose, it would have been much more informative. As stated on page 3, "Manganese is both a required nutrient and a toxic element depending on the route, duration and extent of manganese exposure, as well as the susceptibility of the person exposed." These factors are of course interrelated. There are differences in susceptibility for all chemicals, but these are not important if we are dealing with exposures that are too low to harm even the most susceptible.

I am sure that you will have qualified experts to review various sections of the statement so I will hit only the high spots. Any references cited will refer to the bibliography in the NIEHS statement or in the EPA Health Assessment Document for Manganese(August 1984).

The major points addressed by NIEHS were:

1. Importance of dermal exposure to MMT;
2. Pulmonary symptoms and bronchitis;
3. Neurotoxicity ;
4. Retention in infants and young children;
5. Variations in individual susceptibility
6. Contributions of MMT to airborne Mn.

With respect to <u>skin absorption</u>, the arguments presented by NIEHS clearly do not justify banning MMT. There is no evidence to indicate that the concentrations proposed for gasoline (3½ mg per gallon) would appreciably increase the risks associated with skin exposure to gasoline. Repeated or protracted exposure to gasoline should be avoided, whether or not it contains MMT. There are components, such as benzene, which are present in larger quantities, and which are moe dangerous, than traces of MMT. I know of no problems reported from Canada relevant to this issue.

Turning to pulmonary symptoms and bronchitis, I have read most os the articles pertinent to this and summaries of the rest. These pulmonary reactions have been reported only in populations with exposures far greater than any that could follow gasoline additive use. These are effects that have thresholds of response; drawing conclusions from high exposures regarding low exposures in unjustified. This concern is not relevant to the point at issue.

The discussion on neurotoxicity (pages 8 & 9 and elsewhere) is of interest and clearly of major concern to NIEHS. Again, it is not really relevant to the levels of exposure that would be associated with MMT use. There is no doubt that high concentrations of manganese are neurotoxic. The serious effects of occupational exposures, usually to 5 mg/m^3 or more, are unquestioned. One would also expect that lower concenentrations, e.g. 1 mg/m^3 or more might cause less obvious changes, But we are still dealing with levels which are orders-of-magnitude greater than those associated with MMT as an additive.

It is preposterous to hypothesize that concentrations of Mn in a range essential to human health aould also be producing irreversible neurologic damage. It is also impossible to design an epidemiologic study to test this, since any cohort that was chosen would have to be compared with controls with similar levels of exposure. The recommendation by EPA in 1984 cited by NIEHS related to a possible cohort study of individuals with occupational exposures, much higher than those at issue, aimed at establishing a threshold for regulation of occupational exposures. While a negative result would be important, in my opinion it is not necessary for granting the proposed waiver.

In the discussion of animal studies of neurotoxicty on page 9, I was puzzled by the fact that NIEHS mentioned several positive studies which EPA had said had been "conducted using inadequate experimental conditions". However, they did mention studies also summarized by EPA (1984, page 6-29) which were carefully done, in which rate and primates inhaled Mn_3O_4 for long periods of time with no adverse effects. The first by Ulrich(1975) involved exposures to 11.5, 112.3 and 1152 ug/m^3 for 9 or more months. There were no clinical or histologic signs of neurotoxicity even though Mn blood levels in the most heavily-expoxed animals were 5 times those in controls. Coulston & Griffin(1977) reported on 8 rhesus monkeys exposed continuously for 12 months to 100 ug/m^3 of Mn_3O_4 (derived from combustion of MMT) with no manifestations of toxicity. Two monkeys exposed for 23 weeks to 5000 ug/m^3 by inhalation also showed no clinical or histologic evidence of neurologic damage

Another study of special interest in relation to central nervous system damage is that of Collip et al (1983) will be discussed in the next section.

Possible hypersusceptibility of infants and young children has been an important focus of attention. That infants and young children show relatively high retention of manganese is well-supported by many studies, but there is no evidence to indicate that this is harmful. It rather appears to be consistent with very low levels present in the bodies at birth and probably a need to reach an optimal level.

In the foregoing connection, the work of Collip et al (1983) -eferred to above, deserves special attention. Its importance has been overrated by some who have oversimplified and misinterpreted it. It actually describes two separate studies. The first compares hair Mn levels of infants or children on breast milk (at 4 months), with others on infant formulas containing from 34 to 1000 ug Mn per quart, at 4 weeks, 4 months, 9 months and 3 years. The second study compares hair Mn levels of childredn aged 7 to 10 years in those with so-called "learning disability" with normal children. Several things concern me with respect to this report. The first is reliance upon manganese levels in hair as an index. As NIEHS points out on page 12 of its report, hair provides a very uncertain biomarker. Even if one accepts the hair levels as indices, the Collip study provides little or no evidence associating Mn and "learning disability", or any serious consequences of ingesting Mn. The fact that children who were ingesting milk containing as much as 1 mg per quart had higher Mn levels than those ingesting milk containing 1/100th as much is not remarkable. The important point is: were these amounts harmful?

While the title of the Collip paper includes the term "learning disability" it is important to note that in most of the report they are referred to as "hyperactive" children. The study does not address the question of whether or not hyperactivity had been present at birth. This is a not uncommon type of birth defect. Conceivably it could lead to higher exposures to Mn or higher dietary intake. It certainly does not support any association between Mn and the problem consistent with Mn being the cause.

Another study possibly regarded by some as relevant to Mn and neurotoxicity is that of Newland et al (1987) in which traces of radioactive Mn were found in the heads of primates as long as a year after the inhalation of "trace" amounts of manganese chloride. This highly sensitive method of testing for minute amounts(found in both the head and the chest) cannot be translated into any predictions of possible neurotoxicity.

With respect to individual susceptibility, there is nothing cited by NIESH that appears relevant to the points at issue. It is well-known that people have differing susceptibilities to toxic chemicals. Workers exposed to 5000 µg/m³ of Mn in a factory do not all react similarly. These differences however are not so great as to suggest that individuals exposed within a range necessary to life would have toxic effects similar to those in people exposed to 100 or 1000 times as much.

The foregoing comments apply also to the speculations about the possible effects of an aging population, or iron deficiency anemia and idiopathic hemochromatosis,

I will turn now to the contribution of MMT to airborne fine particles,etc The summary by NIEHS on page 4 is quite misleading, but I am sure that this will be discussed by other reviewers in detail. However I want to call particular attention to the inadequate summary by NIEHS of the study by Davis et al(1988) about Mn in the air of California. NIEHS did not describe the great variations from area to area or site to site. They did not point out the dominant role of naturally occurring Mn upon ambient Mn in most areas. Also, the reported levels, even in Los Angeles,, were really quite low.

I agreee with NIEHS that there are many gaps in our knowledge about manganese and its biologic effects, both beneficial and harmful. This is true about everything in the universe. It should not lead to regulatory paralysis, I hope that I have made it clear that I think the potential benefits from the proposed use of MMT are real, while the hypothetical hazards are speculative.

Sincerely,

W Clark Cooper

W. Clark Cooper, MD

WCC:cc

ATTACHMENT 3

THE ADDITIVE AND DERMAL EXPOSURE

A number of factors affect the rate of percutaneous (skin) absorption of xenobiotics, such as the additive. Percutaneous absorption follows Fick's law of diffusion[1/] which is expressed as:

$$J_s = \frac{K_m D \Delta C_s}{\gamma}$$

Where J_s = is the steady-state flux of the solute ($moles \cdot cm^{-2} \cdot hr^{-1}$)

K_m = is the solute sorbed per milliliter of tissue or solute (solvent-stratum corneum partition coefficient)

D_5= the average membrane diffusion coefficient for solute ($cm^2 \cdot hr^{-1}$)

ΔC_s= Concentration difference of solute across membrane ($moles \cdot cm^{-3}$)

γ = membrane thickness

Two of the factors determining the rate of absorption are relatively fixed while the others are variable. The diffusion coefficient, D, is an inherent property of the substance and the membrane thickness, γ, depends on the genetic make up of the person and the specific area affected. It is also apparent from Fick's Law as it applies to dermal absorption, that the rate of absorption is directly proportional to both the affinity of the solute for the vehicle (solvent), K_m, and the concentration gradient (ΔC_s). Thus, absorption is governed by the vehicle/stratum corneum partition coefficient and the concentration gradient across the stratum corneum. (The stratum corneum is the outer layer of skin). Ethyl has estimated the octanol water coefficient (log P) to be about 3.35 for HiTEC® 3000 meaning that it is several thousand times more soluble in organic solvents than in water. Since HiTEC® 3000 is infinitely soluble in organic solvents such as gasoline, and only soluble to about 10 ppm in water, and since the stratum corneum contains from 10 - 70% water[2/], the solubilities would strongly favor the HiTEC® remaining in the gasoline. The concentration gradient across the stratum corneum also is a determining factor in the rate of absorption. Since the concentration of HiTEC® 3000 in gasoline would be extremely low, approaching zero when compared to other components of gasoline, the rate of absorption must also be very low.

Finally, since J_s is a rate, the amount of substance absorbed also depends on the duration of exposure. Virtually all dermal exposures to gasoline, whether intentional or accidental, are of short duration. Even if someone were to use gasoline as a household degreaser, duration of exposures are generally limited because of other considerations such as flammability.

These factors, i.e. the high solubility of HiTEC® 3000 in gasoline, its low concentration in gasoline and the short duration of dermal exposures to gasoline mean that only extremely small amounts of HiTEC®, if any, could be absorbed dermally. Therefore, there is an extremely low likelihood of accidental poisonings from skin contact with gasoline containing 0.03125 gm Mn/gal HiTEC®.

1/ E. A. Emmett in Casarett and Doull's Toxicology, The Basic Science of Poisons, 3rd Edition; C. D. Klaassen, M. O. Amdur and J. Doull, eds., Macmillan Publishing Co., NY, (1986) p. 416.

2/ Id at 413.

ATTACHMENT 4

ROAD LOAD PARTICULATE EMISSIONS

Using the same particulate testing procedure described in Appendix 3 of Ethyl's Waiver Application dated May 9, 1990, Ethyl has measured both total particulate and manganese emissions from five of the 48 test vehicles used in the Ethyl test program. These cars were cars B3, B5, B6, T1 and T4. Total particulate and manganese emissions from these vehicles were measured at 25 mph, 45 mph, and 60 mph using the particulate tunnel. The results of this testing are shown in Table 1.

The model B cars, with pelleted converters, show that only 1.5 to 2.5 percent of the manganese used in the Additive is exhausted as airborne manganese. The model T cars, using a single monolith converter, exhaust only 5 to 7 percent of the manganese in the Additive as airborne particulate. These low rates of particulate emission, especially at 60 mph, are generally consistent with the results of the particulate testing initially reported to EPA in Ethyl's waiver application.

PARTICULATE EMISSIONS SUMMARY

Road Load Emissions Tests

CAR	MPH	TOTAL GPM	Mn (ugpm)	% INPUT
B3	25	0.00082	16.1	2.6
B5	25	0.00098	16.7	2.5
B6	25	0.00111	14.6	2.4
T1	25	0.00120	50.6	5.8
T4	25	0.00110	47.1	5.1
B3	45	0.00400[1/]	11.4	1.7
B5	45	0.00097	10.5	1.5
B6	45	0.00085	10.0	1.5
T1	45	0.00100	38.2	5.2
T4	45	0.00120	38.9	5.2
B3	60	0.00440	13.8	1.8
B5	60	0.00970	16.4	2.0
B6	60	0.00440	13.6	1.8
T1	60	0.01230	58.4	6.8
T4	60	0.01530	60.6	6.9

1/ Based on an average of two filters which had widely variable weight gains.